Sleep Medicine 15 (2014) 379–384

Contents lists available at ScienceDirect

Sleep Medicine

journal homepage: www.elsevier.com/locate/sleep

Review Article

Periodic limb movements during sleep and their effect on the cardiovascular system: is there a final answer?

Srikant Nannapaneni [a,*], Kannan Ramar [b]

[a] Division of Pulmonary and Critical Care Medicine, Mayo Clinic, Rochester, MN, USA
[b] Center for Sleep Medicine, Mayo Clinic, Rochester, MN, USA

ARTICLE INFO

Article history:
Received 11 October 2013
Received in revised form 4 December 2013
Accepted 11 December 2013
Available online 26 February 2014

Keywords:
Periodic limb movements
Periodic limb movement during sleep
Periodic limb movement disorder
Periodic limb movement index
Cardiovascular
Sleep
Arrhythmias
Heart failure

ABSTRACT

Periodic limb movements during sleep (PLMS) is a sleep-related movement disorder characterized by repetitive limb movements during sleep, seen predominantly in the legs but also occasionally involving the arms. These movements may be associated with arousals that can lead to increases in sympathetic tone, resulting in tachycardia and elevated systolic blood pressure. Chronic sustained tachycardia and elevated systolic blood pressure are known to be associated with the development of arrhythmias, hypertension, left ventricular hypertrophy, and congestive heart failure. However, the data are not entirely clear on whether untreated PLMS is associated with these cardiovascular risks. This review examines the current evidence on whether PLMS has any effect on the cardiovascular system.

1. Introduction

Periodic limb movements during sleep (PLMS) are characterized by periodic, repetitive, highly stereotyped, limb movements mainly of the lower extremities that occur during sleep [1]. PLMS appear to be genetically linked to restless leg syndrome (RLS) and a vast majority of patients (80–88%) with RLS concurrently have PLMS. However, the converse may not be true as PLMS are seen in individuals without RLS and are also observed in individuals with a variety of conditions such as obstructive sleep apnea (OSA), narcolepsy, rapid eye movement (REM) sleep behavior disorder, obesity, depression, fibromyalgia, and diabetes mellitus [2,3]. Similar to RLS, previous studies have shown a 5–8% prevalence of PLMS in the general population. The prevalence appears to increase with age and is likely related to the decrease in dopaminergic activity in the central nervous system [4–6]. Although the prevalence of PLMS increases with age, recent data suggest that the severity may not worsen with age [7]. There appears to be no gender-specific predilection to PLMS [8].

Emerging data suggest that PLMS is associated with an array of chronic medical conditions such as cardiovascular disease, chronic kidney disease, sleep apnea, Parkinson's disease, insomnia and depression [9–12]. Recent research has also focused on increased mortality in patients with congestive heart failure and end-stage renal disease when there is a concomitant diagnosis of PLMS. Specifically, a vast body of literature has been published in the last few years looking at the association between PLMS and cardiovascular disease. It has been postulated that arousals associated with PLMS may activate the sympathetic adrenergic system resulting in heart rate and blood pressure elevations [13,14], and thereby predisposing to adverse cardiovascular events [11,15]. This article critically reviews the currently available literature on the relationship between PLMS and cardiovascular disease outcomes.

2. Diagnosis

Unlike RLS which is a clinical diagnosis based on symptoms, signs, and clinical characteristics, a diagnosis of PLMS is based on the detection of movements during polysomnography (PSG) (Fig. 1). According to the International Classification of Sleep Disorders, 2nd Edition (ICSD-2), PLMS are scored on the PSG if each limb movement is: (i) 0.5–10 s in duration; (ii) electromyogram (EMG) amplitude increases to $\geqslant 8$ μV above the resting baseline;

* Corresponding author. Address: Division of Pulmonary and Critical Care Medicine, Mayo Clinic, 2-115, Old Marion Hall, 1216 2nd Street SW, Rochester, MN 55902, USA. Tel.: +1 507 255 6032.
E-mail address: nannapaneni.srikant@mayo.edu (S. Nannapaneni).

http://dx.doi.org/10.1016/j.sleep.2013.12.014
1389-9457/

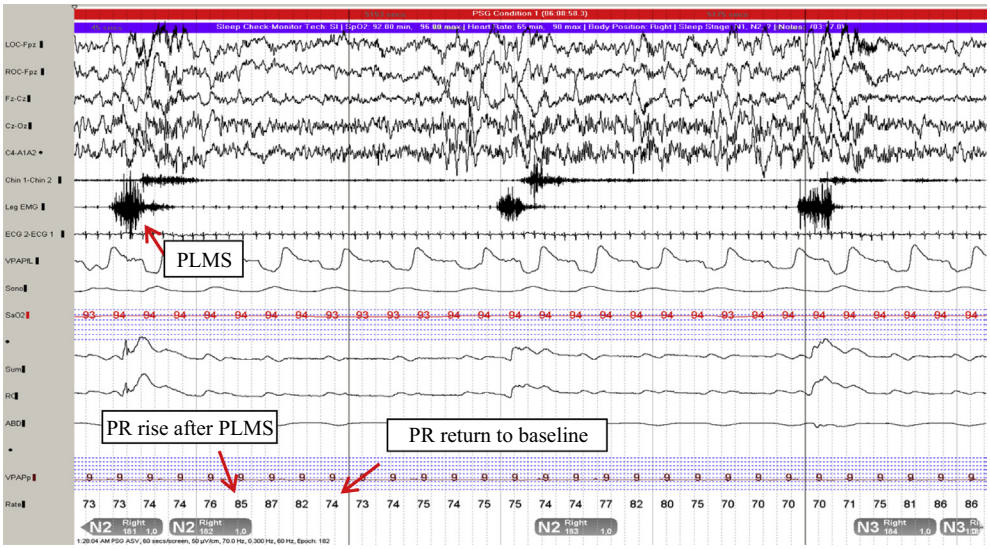

Fig. 1. Hypnogram with a 30 s epoch demonstrating periodic limb movements during sleep (PLMS) with associated increase in pulse rate and arousal. PR, pulse rate.

(iii) occurs in a sequence of four or more movements; and (iv) onset of consecutive movements are >5 s and <90 s apart. Periodic limb movement index (PLMI) is defined as >15 movements/h in adults and >5 movements/h in children [1,16,17]. When these PSG findings are associated with symptoms of sleep disturbance or a complaint of daytime fatigue that cannot be better explained by another sleep disorder, the condition is known as periodic limb movement disorder (PLMD) [1]. Though PLMS most commonly affects the muscles of the lower extremities, it can also affect the arm muscles [18]. EMG activity during PLMS can vary from tonic clonic to myoclonic jerks and can occur only in one leg or on one side of the body or alternate between the two sides [19,20].

3. Pathophysiology of PLMS

The pathophysiological mechanism of PLMS appears to be related to a complex neurologic process involving the dopaminergic system with origins in the brain stem and spinal cord leading to increased autonomic and motor activity [13]. This hypothesis is supported by the fact that drugs that are effective to treat RLS, and which act on the dopaminergic system, are also effective treatment options for most patients with PLMD [21]. In a study by Bucher et al. using functional MRI scans of individuals with PLMS, all the study participants were found to have bilateral cerebellar and red nucleus activation. Areas in the brain stem and pons were also noted to have activation suggesting the possibility of an involuntary mechanism of induction and a subcortical origin for PLMS [22]. Other studies have shown that PLMS are generated within the spinal cord from enhanced spinal cord excitability [23–26].

PLMS appear to occur in cyclical pattern every 20–40 s and predominantly during non-rapid eye movement (NREM) sleep. This observation also leads to the hypothesis that there could be a strong relationship between PLMS and the periodic neurological activity noticed on electroencephalogram (EEG) during NREM sleep known as cyclic alternating pattern (CAP). CAP is associated with increased autonomic activity, and the finding of higher frequency of PLMS during NREM sleep suggests the possibility of a common focus of origin [27]. Additionally, PLMS are more frequent at the beginning of the night (coinciding with NREM sleep stages) and decrease significantly during later sleep phases [28,29] (Fig. 2).

4. Clinical significance

Recent evidence demonstrating a strong genetic link of PLMS through the genes *BTBD9*, *GLO1* and *DNAH8* raises the possibility that there is biological plausibility for this condition [30]. However, there is controversy regarding the clinical significance of PLMS in the absence of RLS symptoms. Patients manifesting PLMS may have complaints of insomnia or daytime fatigue and sleepiness, which, if other sleep disorders are excluded, would give them a diagnosis of PLMD. Although the patient is typically not aware of these limb movements, patients' quality of sleep may be compromised and their bed partner might recognize them. Similarly, these movements might affect the bed partner's quality of sleep and might be the first indication that the patient has PLMS. PLMS can occur without associated EEG micro-arousals, and several studies have supported the argument that PLMS is not associated with daytime symptoms [31,32]. Also, if associated with micro-arousals, the frequency of PLMS does not appear to correlate with objective measures of daytime sleepiness or with indices of disrupted sleep [21]. Studies on the association between PLMS and insomnia (associated with frequent nocturnal arousals) did not find a strong correlation. Specifically, there was no correlation between PLMS and changes in sleep architecture [33] and absence of relationship between PLMS and mean sleep onset latency on MSLT [34]. A more recent study found a positive correlation between PLMS and subjective assessment of tiredness, total sleep time, sleep efficiency, physical fitness and psychological wellbeing [35]. Overall, the non-specific nature of the movements, occurring in association with a wide range of other disorders as well as in otherwise normal elderly people, raises questions as to whether they have any clinical significance of their own or are simply an epiphenomenon of other disorders [31,36,37]. However, more recent research has focused on the association between PLMS and increased risk of mortality in individuals with cardiovascular and renal disease [10,11,38].

5. Effect of PLMS on cardiovascular system

As described earlier, each movement of a PLMS cluster is associated with autonomic responses in the form of discrete elevations in blood pressure and heart rate (Fig. 1). Whether this will

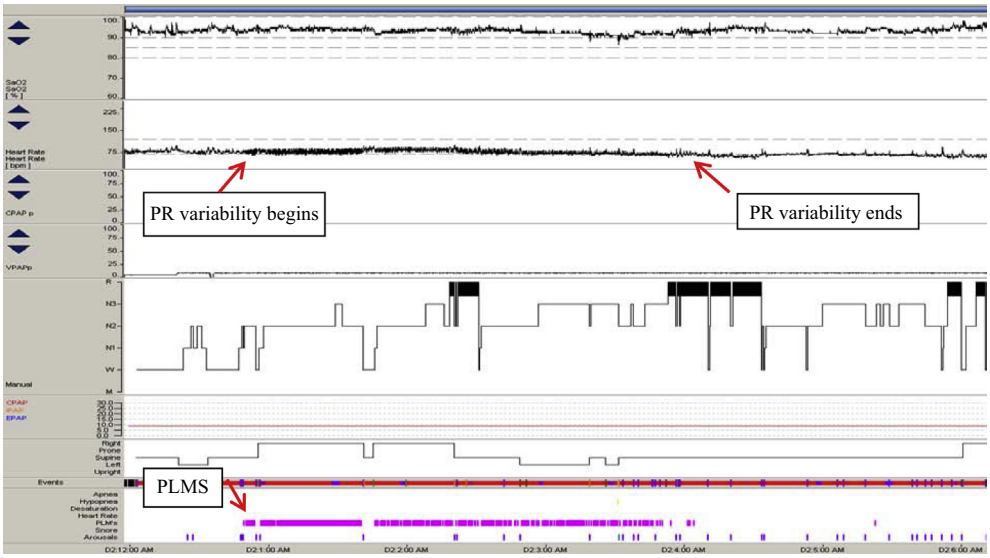

Fig. 2. Hypnogram demonstrating the higher frequency of periodic limb movements during sleep (PLMS) during the early part of the night than later in the night. Associated pulse rate variability is noticeable. PR, pulse rate.

subsequently lead to cardiovascular effects will be reviewed in further detail based on critical analysis of the published literature in this area.

6. Blood pressure

The earliest evidence supporting the link between PLMS and its effect on the cardiovascular system comes from a case report by Ali et al. who documented a 23% rise in systolic blood pressure (SBP) associated with PLMS during PSG in an individual with narcolepsy. However, administration of temazepam to the subject in this study demonstrated that although cortical activity was suppressed, PLMS continued and SBP elevations persisted [39]. More recent studies have shown that PLMS in individuals with RLS are accompanied by discrete increases in systolic (SBP) and diastolic (DBP) blood pressure and in heart rate [13,14,40]. In these studies blood pressure elevation of ~10–20 mmHg and heart rate elevation of up to 10 bpm were noted with each episode of periodic limb movement [13,14]. Pennestri and colleagues demonstrated that PLMS were associated with micro-arousals which lead to a significant elevation in both SBP and DBP [40]. Several other studies have shown the presence of chronic elevations of blood pressure in association with PLMS [4,41,42], even in children [43], but no studies to our knowledge have evaluated the causal relationship between PLMS and essential hypertension. Though, no studies have confirmed the causal relationship between PLMS and hypertension, biologic plausibility may proceed from the hypothesis that PLMS cause brain-stem activation leading to increased sympathetic tone and thereby elevation in SBP, or that the site of origin of PLM is in the brain stem and thereby that secondary activation of the neighboring sympathetic system may result in SBP elevation. However, all these hypotheses need to be confirmed in future studies.

7. Heart rate

In a study by Sforza et al., a significant shortening in the R–R interval (and thereby tachycardia) on electrocardiogram (EKG) was noted in patients with a diagnosis of PLMS, with a more marked decrease in R–R interval in PLMS associated with a micro-arousal compared to PLMS without micro-arousals [44]. PLMS have also been associated with rise in heart rate even in the absence of arousals as noted in a study by Winkelman: the heart rate increase was significantly higher than that seen with leg movements while awake [45]. Similar heart rate increases were noted by Gosselin et al.; they noticed that tachycardia was followed by bradycardia in relation to PLMS onset in patients with RLS. They also noted that the changes in heart rate were age and gender dependent [14,46]. Both these studies noted a significant decrease in heart rate variability in the elderly, suggesting that there is probably an attenuated response to autonomic triggers [47,48]. Gosselin et al. also noted that gender did not influence the degree of heart rate variability but women had longer duration of tachycardia response compared to men. Overall, it is possible that the tachycardia as a result of PLMS may increase the predilection for tachyarrhythmias and also the development of left ventricular hypertrophy (LVH), thereby overall increasing the cardiovascular risk.

8. Left ventricular hypertrophy and congestive heart failure

More recent studies have explored the specific relationship between PLMS and overall cardiovascular disease (CVD). In a study by Mirza et al., individuals with periodic limb movement index (PLMI) > 35/h were noted to have a significantly higher risk for heart failure (odds ratio [OR], 1.62; 95% confidence interval [CI], 1.14–2.30; $P = 0.007$) and mortality (OR, 1.77; 95% CI, 1.12–2.79; $P = 0.014$) compared to those with PLMI < 35/h [38]. After correction for age, sex, and other risk factors for LVH, PLMI > 35/h remained the strongest independent predictor of LVH severity (OR, 2.45; 95% CI, 1.67–3.58; $P < 0.001$) [38].

Results from the Outcomes of Sleep Disorders in Older Men (MrOS) Sleep Study cohort showed that men with PLMI > 30/h and periodic limb movement arousal index (PLMAI) > 5/h experienced a 25% increase in all-cause CVD incidence [10]. In men who were not hypertensive at baseline, PLMI > 30 were associated with an approximately two-fold increase in CVD and peripheral arterial disease incidence. These relationships persisted even after adjusting for age, BMI, apnea–hypopnea index, blood pressure, diabetes mellitus, and hypertension [10]. Incidentally, there was no significant association between PLMI/PLMAI and all-cause CVD in study participants with pre-existing hypertension [10]. The likely explanation for this is that individuals with longstanding

hypertension either had a blunted response to repetitive adrenergic surges associated with PLMS or that study participants may have already been on antihypertensive medications that were not mentioned in these studies [10].

Hanly and Zuberi-Khokhar found a higher prevalence of PLMS in their patients with congestive heart failure (CHF) compared to controls without CHF [49]. This relationship was independent of central sleep apnea. In one of the largest studies evaluating sleep disorders in individuals with CHF, Javaheri noted 20% of the patients had PLMS with an average PLMI of 35/h [50]. However, it is unclear from these studies whether CHF precipitated PLMS or whether PLMS were just an epiphenomenon. Yumino et al. in a recent prospective cohort study noted that patients with PLMI > 5 had lower left ventricular ejection fraction and an increased risk of mortality (hazard ratio, 2.42; 95% CI, 1.16–5.02, $P = 0.018$) [51]. This is one of the first studies to prospectively evaluate the prevalence of PLMS in patients with CHF, also identifying a PLMI threshold that would indicate an increased risk of CVD adverse outcomes.

9. Mechanism of the effect of PLMS on cardiovascular system

Several mechanisms have been proposed to explain the mechanism of PLMS and its effect on the cardiovascular system. The most widely accepted mechanism is that periodic increases in heart rate and blood pressure associated with PLMS during sleep may result from sustained adrenergic surges causing persistent elevation in blood pressures, not only during sleep but also during wakefulness. In addition, PLMS has been associated with unexplained insomnia due to frequent micro-arousals [52]. Studies have demonstrated that individuals with chronic insomnia experience falls in blood pressure during sleep that are commonly called 'dipping' [53,54]. Therefore, insomniacs could have greater blood pressure variability due to increased activation of the sympathetic nervous system due to chronic sleep disruption. Other studies have shown a relationship between sleep disordered breathing (SDB) and PLMS [55], and the relationship between untreated SDB and adverse cardiovascular outcomes such as hypertension, coronary artery disease, LVH and CHF has long been known [56]. These mechanisms along with the independent association of LVH in patients with PLMS may result in increased cardiovascular morbidity over time [57–63]. In the Framingham Heart Study population, patients with LVH were found to have a two-fold higher risk for the development of heart failure compared to those without [60]. Additionally, a strong association has been demonstrated between increased LV mass and increased cardiovascular mortality [59–61]. Though sustained tachycardia over a certain period of time may predispose to LVH, it is not entirely clear whether this mechanism plays a part in PLMS patients [56].

In individuals with CHF, the increased sympathetic nervous system activation during arousals contributes to an increase in left ventricular afterload and elevation in systemic BP, which is an important determinant of survival in individuals with CHF [64,65]. A more recent study by Trotti et al. looked at C-reactive protein (CRP) (which is a marker of inflammation and a risk factor for CVD) and PLMS and noted an elevated level of CRP in individuals with a diagnosis of RLS and concomitant PLMS [66]. CRP has been studied extensively as an inflammatory marker associated with, and predictive of, increased cardiovascular disease risk [67–69]. Although causality is difficult to prove based on these studies, it raises the interesting question of whether PLMS is a pro-inflammatory state and thereby contributes to the increased risk of chronic diseases such as CVD.

Unfortunately, most studies exploring the relationship between PLMS and CVD have been observational or retrospective in nature, except for the MrOS study (Table 1). Most of these studies also based their results on small sample sizes which significantly limits the generalizability of their findings. Based on the methodology of most of these studies it is only possible to infer an association, and causality still remains unproven. It also remains unclear whether individuals with CVD are more prone to developing PLMS or whether PLMS predisposes to increased risk of CVD.

10. Treatment of PLMS and effect on cardiovascular system

Specific treatment guidelines for PLMS are limited due to the lack of long-term prospective studies and the limited number of patients with PLMD who are on treatment. Traditionally, dopamine agonists have been considered to have favorable impact on PLMS due to their efficacy in RLS. Although these drugs cause a reduction in PLMI, their overall efficacy in improving sleep efficiency remains controversial [70,71]. Other medications include selegiline [72], gabapentin [73], magnesium [74], opioids [70,75], clonazepam [76–78], melatonin [79], ropinirole [80] and valproate [81]. Most of these drugs have been tried in small sample studies and demonstrated a reduction in PLMI, but have not shown a significant benefit in improving PLMD. The recent AASM guidelines on the treatment of RLS/PLMD state that there is insufficient evidence to recommend pharmacological therapy for patients diagnosed with PLMD alone [82]. A recent study evaluating the role of pramipexole in treating RLS found that the drug did not abolish the heart rate increase but only reduced the amplitude of heart rate variability induced by PLMS, and returned the heart rate to values similar to those seen in healthy controls [83]. More importantly, the data

Table 1
Studies evaluating the effect of PLMS on the cardiovascular system.

Study	Year	Type of study	CV parameters	Outcome
Ali et al. [39]	1991	Case report	SBP, DBP, HR	Increase in SBP, DBP, HR
Hanly and Zuberi-Khokhar [49]	1996	Case-control	CHF	Higher PLMS
Sforza et al. [44]	1999	Cross-sectional	HR	Tachycardia
Winkelman [45]	1999	Case series	HR	Tachycardia
Gosselin et al. [46]	2003	Cross-sectional	HR	Increase in HR
Javaheri [50]	2006	Prospective observational	CHF	Higher incidence of CHF
Siddiqui et al. [13]	2007	Prospective observational	SBP, DBP, HR	Increase in SBP, DBP, HR
Billars et al. [42]	2007	Prospective observational	SBP	Increase in SBP
Wing et al. [43]	2010	Cross-sectional	SBP	Increase in SBP, DBP
Koo et al. [10]	2011	Prospective observational	CVD, PVD	Increase in CAD, PVD
Yumino et al. [51]	2011	Prospective cohort	CHF	Increase in mortality
Mirza et al. [38]	2013	Retrospective chart review	TTE	LVH
Pennestri et al. [14]	2013	Prospective observational	SBP, DBP, HR	Increase in SBP, DBP, HR

PLMS, periodic limb movements during sleep; CV, cardiovascular; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; CHF, congestive heart failure; CVD, all-cause cardiovascular disease; CAD, coronary artery disease; PVD, peripheral vascular disease; TTE, transthoracic echocardiogram; LVH, left ventricular hypertrophy.

do not support the long-term beneficial effect of using these medications on the cardiovascular system in individuals with PLMS, to affect morbidity or mortality.

11. Conclusion

The clinical significance of PLMS and its relationship to chronic medical conditions such as CVD and CKD remains an area of debate and controversy. Although there is a physiological plausibility to the argument that PLMS increase the risk of CVD by increasing sympathetic nervous system activity resulting in tachycardia, hypertension and LVH, a conclusive association and causality remains to be demonstrated. The current methodology of studies on this association is mostly based on case reports, case series, cross-sectional studies, or observational studies. Further randomized interventional studies specifically targeting treatment of PLMS and evaluating the effect on CVD morbidity and mortality is needed. Until then, a strong recommendation for treatment of PLMS or PLMD specifically to reduce CVD risk cannot be made and each individual patient will have to be assessed individually based on potential risks and benefits or treatment.

Funding sources

None.

Conflict of interest

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: http://dx.doi.org/10.1016/j.sleep.2013.12.014.

References

[1] Berry RB BR, Gamaldo CE, Harding SM, Marcus CL, Vaughn BV. The AASM manual for the scoring of sleep and associated events: rules, terminology and technical specifications, version 2.0. Darien, IL: American Academy of, Sleep Medicine; 2012.
[2] Montplaisir J, Boucher S, Poirier G, Lavigne G, Lapierre O, Lesperance P. Clinical, polysomnographic, and genetic characteristics of restless legs syndrome: a study of 133 patients diagnosed with new standard criteria. Mov Disord 1997;12:61–5.
[3] Al-Alawi A, Mulgrew A, Tench E, Ryan CF. Prevalence, risk factors and impact on daytime sleepiness and hypertension of periodic leg movements with arousals in patients with obstructive sleep apnea. J Clin Sleep Med 2006;2:281–7.
[4] Ohayon MM, Roth T. Prevalence of restless legs syndrome and periodic limb movement disorder in the general population. J Psychosom Res 2002;53:547–54.
[5] Ancoli-Israel S, Kripke DF, Klauber MR, Mason WJ, Fell R, Kaplan O. Periodic limb movements in sleep in community-dwelling elderly. Sleep 1991;14:496–500.
[6] Winkelmann J, Collado-Seidel V, Trenkwalder C. [Restless leg syndrome]. Med Monatsschr Pharm 1999;22:67–71 [review].
[7] Gehrman P, Stepnowsky C, Cohen-Zion M, Marler M, Kripke DF, Ancoli-Israel S. Long-term follow-up of periodic limb movements in sleep in older adults. Sleep 2002;25:340–3.
[8] Scofield H, Roth T, Drake C. Periodic limb movements during sleep: population prevalence, clinical correlates, and racial differences. Sleep 2008;31:1221–7.
[9] Pusalavidyasagar SKJ, Olson EJ, Morgenthaler T. Periodic limb movements in complex sleep apnea syndrome. Open Sleep J 2009;2:43–7.
[10] Koo BB, Blackwell T, Ancoli-Israel S, Stone KL, Stefanick ML, Redline S. Association of incident cardiovascular disease with periodic limb movements during sleep in older men: outcomes of Sleep Disorders in Older Men (MrOS) study. Circulation 2011;124:1223–31.
[11] Benz RL, Pressman MR, Hovick ET, Peterson DD. Potential novel predictors of mortality in end-stage renal disease patients with sleep disorders. Am J Kidney Dis 2000;35:1052–60.
[12] Wetter TC, Collado-Seidel V, Pollmacher T, Yassouridis A, Trenkwalder C. Sleep and periodic leg movement patterns in drug-free patients with Parkinson's disease and multiple system atrophy. Sleep 2000;23:361–7.
[13] Siddiqui F, Strus J, Ming X, Lee IA, Chokroverty S, Walters AS. Rise of blood pressure with periodic limb movements in sleep and wakefulness. Clin Neurophysiol 2007;118:1923–30.
[14] Pennestri MH, Montplaisir J, Fradette L, Lavigne G, Colombo R, Lanfranchi PA. Blood pressure changes associated with periodic leg movements during sleep in healthy subjects. Sleep Med 2013;14:555–61.
[15] Jung HH, Lee JH, Baek HJ, Kim SJ, Lee JJ. Nocturnal hypoxemia and periodic limb movement predict mortality in patients on maintenance hemodialysis. Clin J Am Soc Nephrol 2010;5:1607–13.
[16] Zucconi M, Ferri R, Allen R, Baier PC, Bruni O, Chokroverty S, et al. The official World Association of Sleep Medicine (WASM) standards for recording and scoring periodic leg movements in sleep (PLMS) and wakefulness (PLMW) developed in collaboration with a task force from the International Restless Legs Syndrome Study Group (IRLSSG). Sleep Med 2006;7:175–83.
[17] American Academy of Sleep Medicine. International classification of sleep disorders. 2nd ed. Diagnostic and coding manual. Westchester, IL: AASM; 2005.
[18] Chabli A, Michaud M, Montplaisir J. Periodic arm movements in patients with the restless legs syndrome. Eur Neurol 2000;44:133–8.
[19] Provini F, Vetrugno R, Meletti S, Plazzi G, Solieri L, Lugaresi E, et al. Motor pattern of periodic limb movements during sleep. Neurology 2001;57:300–4.
[20] Lugaresi E, Cirignotta F, Coccagna G, Montagna P. Nocturnal myoclonus and restless legs syndrome. Adv Neurol 1986;43:295–307.
[21] National Heart, Lung and Blood Institute. National Sleep Disorders Research Plan 2003. Bethesda, MD: National Institutes of Health; 2003.
[22] Bucher SF, Seelos KC, Oertel WH, Reiser M, Trenkwalder C. Cerebral generators involved in the pathogenesis of the restless legs syndrome. Ann Neurol 1997;41:639–45.
[23] Rijsman RM, Stam CJ, de Weerd AW. Abnormal H-reflexes in periodic limb movement disorder; impact on understanding the pathophysiology of the disorder. Clin Neurophysiol 2005;116:204–10.
[24] Lee MS, Choi YC, Lee SH, Lee SB. Sleep-related periodic leg movements associated with spinal cord lesions. Mov Disord 1996;11:719–22.
[25] Yokota T, Hirose K, Tanabe H, Tsukagoshi H. Sleep-related periodic leg movements (nocturnal myoclonus) due to spinal cord lesion. J Neurol Sci 1991;104:13–8.
[26] Bara-Jimenez W, Aksu M, Graham B, Sato S, Hallett M. Periodic limb movements in sleep: state-dependent excitability of the spinal flexor reflex. Neurology 2000;54:1609–16.
[27] Terzano MG, Mancia D, Salati MR, Costani G, Decembrino A, Parrino L. The cyclic alternating pattern as a physiologic component of normal NREM sleep. Sleep 1985;8:137–45.
[28] Culpepper WJ, Badia P, Shaffer JI. Time-of-night patterns in PLMS activity. Sleep 1992;15:306–11.
[29] Nicolas A, Michaud M, Lavigne G, Montplaisir J. The influence of sex, age and sleep/wake state on characteristics of periodic leg movements in restless legs syndrome patients. Clin Neurophysiol 1999;110:1168–74.
[30] Stefansson H, Rye DB, Hicks A, Petursson H, Ingason A, Thorgeirsson TE, et al. A genetic risk factor for periodic limb movements in sleep. N Engl J Med 2007;357:639–47.
[31] Hornyak M, Riemann D, Voderholzer U. Do periodic leg movements influence patients' perception of sleep quality? Sleep Med 2004;5:597–600.
[32] Carrier J, Frenette S, Montplaisir J, Paquet J, Drapeau C, Morettini J. Effects of periodic leg movements during sleep in middle-aged subjects without sleep complaints. Mov Disord 2005;20:1127–32.
[33] Karadeniz D, Ondze B, Besset A, Billiard M. Are periodic leg movements during sleep (PLMS) responsible for sleep disruption in insomnia patients? Eur J Neurol 2000;7:331–6.
[34] Coleman RM, Bliwise DL, Sajben N, Boomkamp A, de Bruyn LM, Dement WC. Daytime sleepiness in patients with periodic movements in sleep. Sleep 1982;5(Suppl 2):S191–202.
[35] Haba-Rubio J, Staner L, Krieger J, Macher JP. What is the clinical significance of periodic limb movements during sleep? Neurophysiol Clin 2004;34:293–300.
[36] Roehrs T, Zorick F, Sicklesteel J, Wittig R, Roth T. Age-related sleep–wake disorders at a sleep disorder center. J Am Geriatr Soc 1983;31:364–70.
[37] Silber MH. Sleep-related movement disorders. Continuum 2013;19:170–84.
[38] Mirza M, Shen WK, Sofi A, Jahangir A, Mori N, Tajik AJ. Frequent periodic leg movement during sleep is associated with left ventricular hypertrophy and adverse cardiovascular outcomes. J Am Soc Echocardiogr 2013;26:783–90.
[39] Ali NJ, Davies RJ, Fleetham JA, Stradling JR. Periodic movements of the legs during sleep associated with rises in systemic blood pressure. Sleep 1991;14:163–5.
[40] Pennestri MH, Montplaisir J, Colombo R, Lavigne G, Lanfranchi PA. Nocturnal blood pressure changes in patients with restless legs syndrome. Neurology 2007;68:1213–8.
[41] Espinar-Sierra J, Vela-Bueno A, Luque-Otero M. Periodic leg movements in sleep in essential hypertension. Psychiatry Clin Neurosci 1997;51:103–7.
[42] Billars L, Hicks A, Bliwise D. Hypertension risk and PLMS in restless legs syndrome. Sleep Med 2007;30: A297–A8 [abstract].
[43] Wing YK, Zhang J, Ho CK, Au CT, Li AM. Periodic limb movement during sleep is associated with nocturnal hypertension in children. Sleep 2010;33:759–65.
[44] Sforza E, Nicolas A, Lavigne G, Gosselin A, Petit D, Montplaisir J. EEG and cardiac activation during periodic leg movements in sleep: support for a hierarchy of arousal responses. Neurology 1999;52:786–91.
[45] Winkelman JW. The evoked heart rate response to periodic leg movements of sleep. Sleep 1999;22:575–80.

[46] Gosselin N, Lanfranchi P, Michaud M, Fantini L, Carrier J, Lavigne G, et al. Age and gender effects on heart rate activation associated with periodic leg movements in patients with restless legs syndrome. Clin Neurophysiol 2003;114:2188–95.
[47] Lakatta EG. Determinants of cardiovascular performance. modification due to aging. J Chronic Dis 1983;36:15–30.
[48] Ng AV, Callister R, Johnson DG, Seals DR. Age and gender influence muscle sympathetic nerve activity at rest in healthy humans. Hypertension 1993;21:498–503.
[49] Hanly PJ, Zuberi-Khokhar N. Periodic limb movements during sleep in patients with congestive heart failure. Chest 1996;109:1497–502.
[50] Javaheri S. Sleep disorders in systolic heart failure: a prospective study of 100 male patients. The final report. Int J Cardiol 2006;106:21–8.
[51] Yumino D, Wang H, Floras JS, Newton GE, Mak S, Ruttanaumpawan P, et al. Relation of periodic leg movements during sleep and mortality in patients with systolic heart failure. Am J Cardiol 2011;107:447–51.
[52] Hornyak M, Feige B, Riemann D, Voderholzer U. Periodic leg movements in sleep and periodic limb movement disorder: prevalence, clinical significance and treatment. Sleep Med Rev 2006;10:169–77.
[53] Millar-Craig MW, Bishop CN, Raftery EB. Circadian variation of blood-pressure. Lancet 1978;1(8068):795–7.
[54] Lanfranchi PA, Pennestri MH, Fradette L, Dumont M, Morin CM, Montplaisir J. Nighttime blood pressure in normotensive subjects with chronic insomnia: implications for cardiovascular risk. Sleep 2009;32:760–6.
[55] Haba-Rubio J, Staner L, Krieger J, Macher JP. Periodic limb movements and sleepiness in obstructive sleep apnea patients. Sleep Med 2005;6:225–9.
[56] Somers VK, White DP, Amin R, Abraham WT, Costa F, Culebras A, et al. Sleep apnea and cardiovascular disease: an American Heart Association/American College of Cardiology Foundation Scientific Statement from the American Heart Association Council for High Blood Pressure Research Professional Education Committee, Council on Clinical Cardiology, Stroke Council, and Council on Cardiovascular Nursing. In collaboration with the National Heart, Lung, and Blood Institute National Center on Sleep Disorders Research (National Institutes of Health). Circulation 2008;118:1080–111.
[57] Muxfeldt ES, Cardoso CR, Salles GF. Prognostic value of nocturnal blood pressure reduction in resistant hypertension. Archs Intern Med 2009;169:874–80.
[58] Walters AS, Rye DB. Review of the relationship of restless legs syndrome and periodic limb movements in sleep to hypertension, heart disease, and stroke. Sleep 2009;32:589–97.
[59] Koren MJ, Devereux RB, Casale PN, Savage DD, Laragh JH. Relation of left ventricular mass and geometry to morbidity and mortality in uncomplicated essential hypertension. Ann Intern Med 1991;114:345–52.
[60] Levy D, Garrison RJ, Savage DD, Kannel WB, Castelli WP. Prognostic implications of echocardiographically determined left ventricular mass in the Framingham Heart Study. N Engl J Med 1990;322:1561–6.
[61] Liao Y, Cooper RS, Durazo-Arvizu R, Mensah GA, Ghali JK. Prediction of mortality risk by different methods of indexation for left ventricular mass. J Am Coll Cardiol 1997;29:641–7.
[62] Lorell BH, Carabello BA. Left ventricular hypertrophy: pathogenesis, detection, and prognosis. Circulation 2000;102:470–9.
[63] Haider AW, Larson MG, Benjamin EJ, Levy D. Increased left ventricular mass and hypertrophy are associated with increased risk for sudden death. J Am Coll Cardiol 1998;32:1454–9.
[64] Cohn JN, Levine TB, Olivari MT, Garberg V, Lura D, Francis GS, et al. Plasma norepinephrine as a guide to prognosis in patients with chronic congestive heart failure. N Engl J Med 1984;311:819–23.
[65] Francis GS, Cohn JN, Johnson G, Rector TS, Goldman S, Simon A. Plasma norepinephrine, plasma renin activity, and congestive heart failure. Relations to survival and the effects of therapy in V-HeFT II. The V-HeFT VA Cooperative Studies Group. Circulation 1993;87(6 Suppl.):VI40–V8.
[66] Trotti LM, Rye DB, De Staercke C, Hooper WC, Quyyumi A, Bliwise DL. Elevated C-reactive protein is associated with severe periodic leg movements of sleep in patients with restless legs syndrome. Brain Behav Immun 2012;26:1239–43.
[67] Kaptoge S, Di Angelantonio E, Pennells L, Wood AM, White IR, Gao P, et al. C-reactive protein, fibrinogen, and cardiovascular disease prediction. N Engl J Med 2012;367:1310–20.
[68] Ridker PM. Clinical application of C-reactive protein for cardiovascular disease detection and prevention. Circulation 2003;107:363–9.
[69] Sabatine MS, Morrow DA, Jablonski KA, Rice MM, Warnica JW, Domanski MJ, et al. Prognostic significance of the Centers for Disease Control/American Heart Association high-sensitivity C-reactive protein cut points for cardiovascular and other outcomes in patients with stable coronary artery disease. Circulation 2007;115:1528–36.
[70] Kaplan PW, Allen RP, Buchholz DW, Walters JK. A double-blind, placebo-controlled study of the treatment of periodic limb movements in sleep using carbidopa/levodopa and propoxyphene. Sleep 1993;16:717–23.
[71] de Mello MT, Poyares DL, Tufik S. Treatment of periodic leg movements with a dopaminergic agonist in subjects with total spinal cord lesions. Spinal Cord 1999;37:634–7.
[72] Grewal M, Hawa R, Shapiro C. Treatment of periodic limb movements in sleep with selegiline HCl. Mov Dis 2002;17:398–401.
[73] Garcia-Borreguero D, Larrosa O, de la Llave Y, Verger K, Masramon X, Hernandez G. Treatment of restless legs syndrome with gabapentin: a double-blind, cross-over study. Neurology 2002;59:1573–9.
[74] Hornyak M, Voderholzer U, Hohagen F, Berger M, Riemann D. Magnesium therapy for periodic leg movements-related insomnia and restless legs syndrome: an open pilot study. Sleep 1998;21:501–5.
[75] Kavey N, Walters AS, Hening W, Gidro-Frank S. Opioid treatment of periodic movements in sleep in patients without restless legs. Neuropeptides 1988;11:181–4.
[76] Saletu M, Anderer P, Saletu-Zyhlarz G, Prause W, Semler B, Zoghlami A, et al. Restless legs syndrome (RLS) and periodic limb movement disorder (PLMD): acute placebo-controlled sleep laboratory studies with clonazepam. Eur Neuropsychopharmacol 2001;11:153–61.
[77] Ohanna N, Peled R, Rubin AH, Zomer J, Lavie P. Periodic leg movements in sleep: effect of clonazepam treatment. Neurology 1985;35:408–11.
[78] Edinger JD, Fins AI, Sullivan RJ, Marsh GR, Dailey DS, Young M. Comparison of cognitive-behavioral therapy and clonazepam for treating periodic limb movement disorder. Sleep 1996;19:442–4.
[79] Kunz D, Bes F. Exogenous melatonin in periodic limb movement disorder: an open clinical trial and a hypothesis. Sleep 2001;24:183–7.
[80] Saletu M, Anderer P, Saletu B, Hauer C, Mandl M, Semler B, et al. Sleep laboratory studies in periodic limb movement disorder (PLMD) patients as compared with normals and acute effects of ropinirole. Hum Psychopharmacol 2001;16:177–87.
[81] Ehrenberg BL, Eisensehr I, Corbett KE, Crowley PF, Walters AS. Valproate for sleep consolidation in periodic limb movement disorder. J Clin Psychopharmacol 2000;20:574–8.
[82] Aurora RN, Kristo DA, Bista SR, Rowley JA, Zak RS, Casey KR, et al. The treatment of restless legs syndrome and periodic limb movement disorder in adults – an update for 2012: practice parameters with an evidence-based systematic review and meta-analyses: an American Academy of Sleep Medicine Clinical Practice Guideline. Sleep 2012;35:1039–62.
[83] Manconi M, Ferri R, Zucconi M, Clemens S, Rundo F, Oldani A, et al. Effects of acute dopamine-agonist treatment in restless legs syndrome on heart rate variability during sleep. Sleep Med 2011;12:47–55.